Diabetes, Glycemic Control, and Risk of Tuberculosis

A population-based case-control study

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OBJECTIVE—To examine the association between diabetes, glycemic control, and risk of tuberculosis (TB).

RESEARCH DESIGN AND METHODS—We conducted a population-based case-control study in Northern Denmark. Cases of active TB were all individuals with a first-time principal hospital diagnosis of TB between 1980 and 2008. Each case subject was matched with up to five population control subjects with similar age, sex, place and length of residence in Denmark, and country of emigration. We computed odds ratios (ORs) for a first-time TB diagnosis among people with and without diabetes using regression to control for other comorbidities, alcoholism, immunosuppressive medications, and socioeconomic markers.

RESULTS—We identified 2,950 patients, including 156 diabetic individuals (5.3%), with active TB, and 14,274 population control subjects, of which 539 had diabetes (3.8%). The adjusted OR for active TB among subjects with diabetes was 1.18 (95% CI 0.96–1.45) compared with nondiabetic individuals. We found a similar risk increase from diabetes in the 843 (29%) TB case subjects who were immigrants; adjusted OR = 1.23 (95% CI 0.78–1.93). In a subset with laboratory data, diabetic individuals with an HbA_{1c} <7.0, 7–7.9, and ≥8.0% had ORs of 0.91 (0.51–1.63), 1.05 (0.41–2.66), and 1.19 (CI 0.61–2.30), respectively, compared with individuals without diabetes.

CONCLUSIONS—In the low TB–burden country of Denmark, the TB risk increase associated with diabetes is substantially lower than previously suggested. We found no evidence for any association between TB and dysglycemia.

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The number of people in the world with diabetes is projected to increase to 366 million by 2030 with the fastest increase in low- to middle-income countries (1). At the same time, these countries are dealing with the highest burden of tuberculosis (TB) in the world (2). The strength of any association between diabetes, dysglycemia, and risk of TB remains debated (3). In the first half of the 20th century, when antidiabetic treatment was limited, diabetes seemed to be a clinically well-recognized risk factor for TB (4). Recent studies showed that the innate immune system is impaired by high levels of blood glucose (5,6), and that diabetic individuals have a 25–75% increased risk of pneumonia (7). A recent population-based cohort study from Hong Kong (8) and a review of 13 previous smaller observational studies (9) found diabetes to be associated with increased risk of TB, with relative risk estimates varying considerably from 1.2 to 7.8, with the lowest estimates reported in the larger studies. Only two studies have focused on the role of dysglycemia (8,10). Leung et al. (8) found that among elderly individuals with diabetes, those with HbA_{1c} ≥7% had an adjusted TB relative risk of 3.1 (95% CI 1.6–5.9) compared with those with HbA_{1c} <7%, whereas Pablos-Mendez et al. (10) found that only "complicated" or "poorly controlled" diabetes was associated with increased TB risk.

As the prevalence of diabetes increases globally, it is important to clarify any association with TB so the strategy for controlling TB can be appropriately targeted (2,3). We examined whether diabetes and glycemic control are associated with an increased risk of TB in a large, population-based case-control study in Denmark.

RESEARCH DESIGN AND METHODS

Setting

We conducted this study in Northern Denmark, with 1.8 million inhabitants (~30% of the Danish population). Since 1977, complete computerized hospitalization records have been available for this population. Our study period began on 1 January 1980, thus providing at least 3 years of hospitalization history for all study participants. We included subjects through 31 December 2008. Denmark is a welfare state, with tax-supported universal access to health services (11). Accurate linkage of all databases used in this study was possible using the unique central personal registry number assigned to each Danish citizen.

Patients with TB

Patients with TB in Denmark receive their diagnosis and treatment from public hospitals either during inpatient admission or at a hospital outpatient clinic. According to Danish guidelines, all individuals suspected for TB in Denmark should be referred to a hospital and isolated until the TB diagnosis is clear (12). We identified all patients with a first-time hospital contact with a principal diagnosis of TB in

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Northern Denmark during the study period using the Danish National Registry of Patients (DNRP) (13), which covers all Danish hospitals. The DNRP contains data on all hospitalizations since 1977 and on all hospital outpatient clinic visits since 1995. Each discharge is associated with one principal diagnosis (i.e., the condition chiefly responsible for occasioning the admission) and one or more secondary diagnoses (i.e., other conditions that had bearing on the care) classified by physicians according to the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and ICD-10 thereafter (13).

To reduce the impact of potential coding errors, we initially retrieved a sample of 100 hospital records with first-time inpatient or outpatient principal or secondary diagnosis of TB in a subset of Northern Denmark, the former North Jutland County, from 1994 through 2006. We selected all TB patients with a history of diabetes (n = 42; see diabetes algorithm below) and a random sample of the remaining TB patients (n = 58) for a detailed review. We estimated the positive predictive value (PPV) as the percentage of TB episodes that fulfilled the European Union TB case classification (14). Thus, cases of active TB either had *Mycobacterium tuberculosis* complex (except *M. bovis* Bacillus Calmette-Guérin) isolated from a clinical specimen, or had *M. tuberculosis* DNA detected by PCR analysis, acid-fast bacilli demonstrated by direct microscopy, granuloma detected by histology, or had signs, symptoms, and/or radiological findings consistent with active TB in any site. All case subjects had anti-TB treatment instituted with the decision to treat with a full course of anti-TB therapy.

On the basis of the results of our review (see RESULTS), we included in our study all patients with a first-time principal TB diagnosis who lived within Northern Denmark on the TB diagnosis date (n = 3,558). We excluded patients who had lived for <6 months in the region (n = 240) to allow time for identification of diabetes exposure and confounders, and pediatric patients <15 years (n = 280). This gave us a unique population of 3,038 adults with a first-time hospital diagnosis of active TB (see flowchart in Supplementary Fig. 1). For a subset of this population living in former North Jutland and Aarhus counties from 1997 onwards, we also had data from the microbiological TB registry at the Statens Serum Institute in Copenhagen (15) to ascertain culture-confirmed TB case subjects.

Population control subjects

From the Danish Civil Registration System, a nationwide registry of all Danish residents, we randomly chose up to five population control subjects for each case subject, individually matched on age (±5 years), sex, country of origin (if immigrant status), and place and length of residence (±1 year) in Northern Denmark. We selected control subjects using risk-set sampling; matched control subjects for each TB case subject were obtained by random sampling from the set of people in the general population who were still at risk for becoming a TB case subject (i.e., who had no TB diagnosis in the DNRP) at the time that the corresponding TB case subject was diagnosed. For 88 case subjects (3%), we were unable to find any control subject with an exact match, leaving 2,950 TB case subjects and 14,274 matched control subjects for analysis.

Diabetes and glycemic control

We identified individuals with diabetes before their index date by a validated algorithm from three databases as previously described in detail (7): the DNRP, the Aarhus University Prescription Database (16), and the Danish National Health Insurance Service Registry. Diabetes was defined as previous in- or outpatient hospital contact involving diabetes, any use of oral antidiabetes drugs or insulin, at least one visit to a chiropodist for diabetes foot care, at least five glucose-related services in general practice in 1 year, or at least two glucose-related services each year during 5 subsequent years (7). Diabetic patients under the age of 30 years using insulin monotherapy and never using oral antidiabetes medications were classified as type 1. The remaining diabetic patients were classified as type 2. For each individual, we computed the time elapsed between the first record of diabetes and the index date.

For the subset of case subjects and control subjects living in former North Jutland and Aarhus counties from 1997 onwards, where detailed laboratory data were available (7), we obtained information on HbA_{1c} measurements associated with diabetes. We used the most recent measurement of HbA_{1c} within 12 months before the index date.

Confounding factors

To control for confounding by conditions potentially associated with both diabetes and TB, we retrieved data on 19 major comorbid disease categories, as evidenced in the Charlson comorbidity index, diagnosed before the index date. Diseases included (among others) heart disease, pulmonary diseases, including chronic obstructive pulmonary disease, cancer, liver disease, and HIV/AIDS (7). We adjusted separately for the presence of alcoholism-related disorders. Furthermore we used information from the Civil Registration System to adjust for each person's urbanization (rural, provincial town, or city), marital status (married, never married, divorced or widowed, or unknown), and number of children <15 years (0, 1–3, or ≥4). For the subset of people living in North Jutland and Aarhus counties from 1997 onwards, we additionally adjusted for use of inhalation corticosteroids, peroral corticosteroids, other immunosuppressive medications, and proton pump inhibitors, all within 1 year before the index date. ICD codes and Anatomical Therapeutic Chemical Classification System codes are provided in Supplementary Table 1.

Statistical analysis

We used conditional logistic regression to estimate odds ratios (ORs) with 95% CIs as a measure of incidence rate ratios of first-time hospital diagnosis of active TB among diabetic and nondiabetic subjects. In the subset with laboratory data, diabetes was furthermore categorized according to type and level of HbA_{1c} (<7.0, 7.0–7.9, ≥8.0%, or unknown). We adjusted for confounders as described above. Stratified analyses were performed by sex, age group (15–39, 40–64, 65–79, or ≥80 years), calendar time period, and immigrants versus Danish residents. All analyses were conducted using STATA software. The study was approved by the Danish Data Protection Agency (Record 2008-41-2436).

RESULTS

Descriptive data

The study included 2,950 patients with a first-time hospital diagnosis of active TB, including 156 diabetic individuals (5.3%), and 14,274 population control subjects, of which 539 had diabetes (3.7%). The median time between the first record of diabetes and the TB/index date was 3.7 years (interquartile range [IQR] = 1.3–7.3 years) for TB case subjects and 3.6 years (1.7–7.9 years) for population control subjects.

Characteristics of TB case subjects and control subjects are shown in Table 1. Of these subjects, 53.1% were male, and the median age (IQR) was 54 years (35–71 years) among case subjects and 55 years

Table 1—*Demographic and clinical characteristics of case subjects with a first-time hospital diagnosis of TB and population control subjects from Northern Denmark, 1980–2008*

Characteristic	Case subject	Population control subject
n	2,950	14,274
Diabetes		
Absent	2,794 (94.7)	13,735 (96.2)
Present	156 (5.3)	539 (3.8)
Sex		
Male	1,567 (53.1)	7,610 (53.3)
Female	1,383 (46.9)	6,664 (46.7)
Age (years) (median [IQR])	54.4 (35.2–70.5)	54.8 (35.3–70.8)
Charlson comorbidity index		
Index low (0)	2,111 (71.6)	12,179 (85.3)
Index medium (1–2)	691 (23.4)	1,813 (12.7)
Index high (3+)	148 (5.0)	282 (2.0)
HIV infection	3 (0.1)	13 (0.1)
Alcoholism-related conditions	268 (9.1)	216 (1.5)
Marital status		
Married	1,513 (51.3)	8,549 (59.9)
Never married	660 (22.4)	2,705 (19.0)
Divorced or widowed	777 (26.3)	3,020 (21.2)
Children aged <15 years		
0 children	2,304 (78.1)	10,852 (76.0)
1–3 children	553 (18.8)	3,028 (21.2)
4+ children	93 (3.2)	394 (2.8)
Degree of urbanization		
Rural	454 (15.4)	2,569 (18.0)
Provincial town	1,312 (44.5)	6,960 (48.8)
City	1,184 (40.1)	4,745 (33.2)
Origin		
Denmark	2,107 (71.4)	10,535 (73.8)
Immigrant	843 (28.6)	3,739 (26.2)
Immigrants, origin		
Somalia	396 (47.0)	1,906 (51.0)
Vietnam	99 (11.7)	444 (11.9)
Sri Lanka	42 (5.0)	182 (4.9)
Turkey	35 (4.2)	151 (4.0)
Afghanistan	28 (3.3)	110 (2.9)
Iran	23 (2.7)	99 (2.6)
Iraq	20 (2.4)	84 (2.2)
Lebanon	20 (2.4)	96 (2.6)
Other	180 (21.4)	667 (17.8)
Immigrants, time since arrival, (years) (median [IQR])	3.8 (1.9–7.5)	3.7 (1.8–7.2)
Subset 1997–2008	1,019	4,856
Immunosuppressants		
Systemic steroid therapy	71 (7.0)	179 (3.7)
Other	15 (1.5)	18 (0.4)
Inhalation steroid therapy	97 (9.5)	133 (2.7)
Proton pump inhibitor therapy	149 (14.6)	315 (6.5)

Data are *n* (% of total), unless otherwise indicated.

(35–71 years) among control subjects. A total of 843 (29%) of the TB patients were immigrants living in Northern Denmark for at least 6 months, with a median duration of 3.8 years from arrival (immigrant control subjects, 3.7 years). Among immigrants, 47% came from Somalia. TB case subjects had more comorbidity than population control subjects, in particular, alcoholism-related disorders, chronic obstructive pulmonary disease, chronic heart failure, cancer, and renal disease. TB case subjects also used more immunosuppressants, including corticosteroids, and were more likely to be unmarried and to live in the city (Table 1).

Validation of TB diagnoses

In the reviewed sample of 100 patients diagnosed with a first-time hospital diagnosis of active TB, 65 patients fulfilled our criteria, corresponding to a PPV of 65.0% (95% CI 54.8–74.3). In total, 35 TB diagnoses had to be rejected as false positives because of either plain coding errors (n = 6), suspected but later dismissed TB diagnosis (n = 17), or presence of previously active but not currently active TB (n = 12). Principal TB diagnoses had a high PPV of 56/70 = 80.0% (68.7–88.6), whereas the PPV of secondary diagnoses was much lower; only 9/30 = 30.0% (14.7–49.4). Diabetic patients had an only slightly lower PPV (74.1% [53.7–88.9]) of principal TB diagnoses than nondiabetic patients (83.7% [69.3–93.2]). We concluded that the validity of principal diagnoses of TB in the DNRP was sufficient for our study purposes.

Risk estimates

The OR for a first-time hospital diagnosis of active TB in diabetic patients was 1.44 (95% CI 1.19–1.74). After controlling for confounding factors, the OR substantially decreased to 1.18 (0.96–1.45) (Table 2). The adjusted OR for TB tended to be higher for type 1 diabetes (2.59 [0.44–15.29]), but the estimate was imprecise. Presence of other comorbidities was the strongest confounder of the association between diabetes and TB risk, reducing the crude OR from 1.44 to 1.21. Thus, half of the apparent effect of diabetes may have been caused by a higher prevalence of comorbidities, notably cardiopulmonary disease.

In the subset of 1,019 TB case subjects and 4,856 subjects from Aarhus and North Jutland counties in the 1997–2008 period, where both prescription data, laboratory data, and microbiological TB registry data were available, the association between diabetes and TB was even weaker with crude OR = 1.25 (95% CI 0.92–1.69) and adjusted OR = 1.02 (0.73–1.44) (Table 2). Compared with nondiabetic individuals, diabetic individuals with an HbA_{1c} <7.0% had an OR of 0.91 (0.51–1.63), whereas the OR for those with an HbA_{1c} of 7.0–7.9% was 1.05 (0.41–2.66) and for an HbA_{1c} of ≥8% was 1.19 (0.61–2.30) (Table 2). Although the ORs appeared to increase with successive increases in

Table 2—*ORs for a first-time hospital diagnosis of active TB associated with diabetes*

Exposure	Case subject	Matched population control subject	Crude OR (95% CI)	Adjusted OR (95% CI)*
Diabetes				
Absent	2,794 (94.7)	13,735 (96.2)	1.0 (ref.)	1.0 (ref.)
Present	156 (5.3)	539 (3.8)	1.44 (1.19–1.74)	1.18 (0.96–1.45)
Diabetes type				
Diabetes absent	2,794 (94.7)	13,735 (96.2)	1.0 (ref.)	1.0 (ref.)
Type 1	3 (0.1)	6 (0.04)	2.94 (0.64–13.60)	2.59 (0.44–15.29)
Type 2	153 (5.2)	533 (3.7)	1.43 (1.18–1.73)	1.17 (0.95–1.44)
Subset 1997–2008†				
Diabetes				
Absent	958 (94.0)	4,620 (95.1)	1.0 (ref.)	1.0 (ref.)
Present	61 (6.0)	236 (4.9)	1.25 (0.92–1.69)	1.02 (0.73–1.44)
HbA_{1c} (%)				
Diabetes absent	958 (94.0)	4,620 (95.1)	1.0 (ref.)	1.0 (ref.)
<7.0	18 (1.8)	74 (1.5)	1.18 (0.70–2.01)	0.91 (0.51–1.63)
7.0–7.9	7 (0.7)	31 (0.6)	0.99 (0.43–2.29)	1.05 (0.41–2.66)
≥8.0	16 (1.6)	47 (1.0)	1.61 (0.88–2.92)	1.19 (0.61–2.30)
Unknown	20 (2.0)	84 (1.7)	1.20 (0.73–1.99)	1.02 (0.58–1.78)
Subset 1997–2008, microbiologically confirmed cases‡				
Diabetes				
Absent	568 (96.1)	2,706 (96.5)	1.0 (ref.)	1.0 (ref.)
Present	23 (3.9)	99 (3.5)	1.08 (0.67–1.75)	0.95 (0.55–1.64)

Data are *n* (%), unless otherwise indicated. Ref, reference. *OR adjusted for level of comorbidity, alcoholism-related disorders, marital status, number of children under the age of 15 years, and degree of urbanization; for subsets 1997–2008, also adjusted for systemic immunosuppressants, inhalation steroid therapy, and proton pump inhibitor therapy prior to the index diagnosis. †Includes 1,019 TB case subjects and 4,856 matched control subjects in North Jutland and Aarhus counties from 1997 to 2008. ‡Includes 591 microbiologically confirmed TB case subjects and 2,805 matched control subjects in North Jutland and Aarhus counties from 1997 to 2008.

HbA_{1c}, this trend was not statistical significant (likelihood ratio test $P = 0.78$).

Adult diabetic individuals under age 40 were 1.86 (95% CI 0.88–3.94) times more likely to have a hospital contact with TB diagnosis than nondiabetic individuals of similar age, whereas the relative risk decreased in elderly individuals with diabetes, with risk estimates close to 1 in people aged 65 or older (Table 3). Risk estimates tended to be higher in women than in men and were highest in the early years of the study period. The adjusted TB ORs associated with diabetes were similar among native Danes (1.17 [0.93–1.46]) and immigrants (1.23 [0.78–1.93]).

Of 1,019 TB case subjects with hospital contact in North Jutland and Aarhus counties from 1997 to 2008, 591 (58.0%) were culture-confirmed TB case subjects in the Statens Serum Institute Registry. Confirmed TB case subjects were younger (median age 39.4 years) than all TB case subjects during the same period (44.8 years). A proportion of 3.9% had diabetes versus 3.5% of their control subjects, corresponding to a similar OR for culture-confirmed TB than for any recorded TB (Table 2).

Finally, we reran our analyses while also including diabetes diagnoses made at the hospital diagnosis date per index date of TB. The prevalence of recorded diabetes rose from 5.3 to 6.0% in TB case subjects and from 3.7 to 3.9% in population of control subjects, corresponding to a slightly higher adjusted OR of 1.36 (95% CI 1.12–1.66) associated with diabetes.

CONCLUSIONS—The findings from this population-based study suggest that diabetic patients in Denmark have only a

Table 3—*ORs for TB according to diabetes, stratified by age, sex, time period, and county of origin, and ORs for microbiologically confirmed TB according to diabetes*

	Crude OR (95% CI)	Adjusted OR* (95% CI)
Age (years)		
15–39	1.90 (0.92–3.92)	1.86 (0.88–3.94)
40–64	2.06 (1.50–2.84)	1.48 (1.03–2.13)
65–79	1.14 (0.84–1.55)	0.97 (0.70–1.34)
80+	1.15 (0.73–1.82)	1.04 (0.65–1.67)
Sex		
Male	1.34 (1.02–1.75)	1.08 (0.81–1.44)
Female	1.56 (1.19–2.04)	1.30 (0.98–1.73)
Time period		
1980–1987	1.79 (1.17–2.73)	1.37 (0.88–2.14)
1988–1996	1.37 (0.96–1.97)	1.14 (0.78–1.66)
1997–2008	1.37 (1.05–1.78)	1.14 (0.85–1.51)
Origin		
Denmark	1.48 (1.19–1.82)	1.17 (0.93–1.46)
Immigrant	1.32 (0.85–2.03)	1.23 (0.78–1.93)

*OR adjusted (except when stratified by variable) for level of comorbidity, alcoholism-related disorders, marital status, number of children under the age of 15, and degree of urbanization.

modestly increased risk of TB compared with other individuals. We found no evidence for an association between TB and glycemic control among people with diabetes and TB.

Our risk estimates for TB from diabetes are lower than in many previous, mainly clinic-based studies. A systematic review from 2007 included nine case-control and cohort studies and found that diabetes was consistently associated with an increased risk of TB, however with widely differing relative risk estimates between 1.5 and 7.8 (17). A newer meta-analysis from 2008 included 13 epidemiologic studies (9). This review found that diabetes was associated with a 3.1 (2.3–4.3) times elevated risk of TB in three cohort studies, and with ORs between 1.16 and 7.83 in 10 case-control or cross-sectional studies. ORs were 1.50, 1.61, and 1.65, respectively, in the three largest case-control studies, and the increasing risk estimates with decreasing study size indicate some publication bias. Most studies were unable to properly adjust for confounding factors. In a large case-control analysis of 5,290 hospitalized TB case subjects by Pablos-Mendez et al. (10) among ethnic groups in California, adjusted TB ORs from diabetes were 0.93 (95% CI 0.78–1.09) among blacks, 1.31 (1.19–1.45) among whites, and 2.95 (2.61–3.33) among Hispanics, respectively. Leung et al. (8) followed a cohort of 42,116 elderly patients in Hong Kong; diabetes was associated with adjusted TB hazard ratios of 1.77 (1.41–2.24) for any active TB and 1.89 (1.48–2.42) for pulmonary TB. Interestingly, diabetic subjects with HbA_{1c} <7% at enrollment were not at increased risk, however. New studies from Australia and the U.S. corroborate our findings of a modest association between diabetes and TB before comorbidity adjustment. In a historical follow-up study from New South Wales, the age-, sex-, and ethnicity-adjusted risk estimate of TB in people with diabetes was 1.30 (0.93–1.82) (18). In a U.S. cross-sectional study based on data from the 2000–2005 National Health Interview Survey, diabetic individuals had an age- and ethnicity-adjusted OR of 1.4 (1.0–2.0) for history of TB (19). In conclusion, it seems that newer and larger studies of the issue tend to find only modestly increased TB risk estimates associated with diabetes. Some older studies may have been hampered by selection and surveillance bias, and lack of sufficient confounder adjustment. Alternatively, older studies may include more severe or more poorly controlled diabetes patients who may have a higher TB risk than patients with mild and well-controlled diabetes. Thus, we observed a stronger diabetes–TB association during the 1980s versus more recent years in our own material.

We observed a slight, statistically nonsignificant increase in ORs with successive increases in HbA_{1c}. We had rather few individuals with highly elevated HbA_{1c} in our dataset, which might be attributed to the limited time period for which this data were available, but also to the fact that all individuals with diabetes have free access to high quality care in Denmark.

It is currently not clear if diabetes makes individuals more susceptible to initial *M. tuberculosis* infection or increases the development of active TB disease from latent infection (3). However, relapsing TB is probably rare in our data; in a recent Danish 13-year series, <2% TB episodes were recurrences (20). Diabetic patients have increased risk of several types of serious infections (7,21–23), and their innate immune system seems to be impaired by a high blood glucose level and conversely improved by hyperinsulinemia (5,6). Experimental studies on rats infected with *M. tuberculosis* (24) showed that activation of alveolar macrophages was impaired in diabetic rats because of a lower production of nitric oxide. Similar findings were reported by Yamashiro et al. (25), who, in addition, found a lower expression of the Th1-related cytokines interleukin-12 and interferon-γ. It is now well substantiated from large epidemiological studies that diabetes confers a modestly (~1.5 times) increased risk for upper and lower respiratory tract infections (7,21–23) compared with two to three times increased risks for severe urinary tract infections and wound infections (21,22).

Our population-based design in the setting of a universal healthcare system largely eliminated selection biases stemming from selective inclusion of specific hospitals, health insurance systems, patients, or age groups. Increased surveillance of diabetic patients may have led to overestimation of TB risk, and on the other hand, certain at-risk populations such as immigrants and homeless people might have gone undiagnosed. Nevertheless, active TB is typically accompanied by severe symptoms that would eventually lead to physician contact for diagnosis and treatment in a setting with free and unrestricted access to health care.

As accurate linkage among comprehensive databases was possible, we avoided recall bias, which may have affected prior studies. Because of the insidious onset of diabetes, we might have missed some diabetic patients. Also, early unspecific symptoms of TB might lead a future TB case subject to seek medical help and hence be diagnosed with previously undetected diabetes. When we reran our analyses also counting diabetes diagnoses made at the same time as the TB diagnosis, we found a somewhat stronger association.

Immigrants in general have a substantially higher incidence of TB compared with Danish people (14,15), and TB often occurs soon after arriving in Denmark (15). The probability of having diabetes detected may have been lower in immigrants than Danes in our study because of shorter observation or different health care–seeking behavior. However, the observation time for diabetes since arrival was similar in immigrant TB case subjects and immigrant control subjects. Because of the relatively short observation time in immigrants, we could not validly examine the impact of longstanding diabetes, which is known to increase the risk of hospitalized pneumonia (7).

Although we were able to control for substantial confounding, our results may still be affected by confounding from unmeasured variables, including lifestyle and other exogenous factors such as smoking status, living standard, BMI, history of imprisonment, homelessness, traveling in high-endemic TB areas, and history of Bacillus Calmette-Guérin vaccination. As low socioeconomic status and unhealthy lifestyle are associated with diabetes, unmeasured confounding would most likely cause an overestimation of the association between diabetes and TB, not changing our conclusions.

In conclusion, our population-based data show a very modest association between diabetes and risk of TB in Denmark, corroborating newer studies from highly developed countries. We found no evidence for any association with glycemic control.

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A.L. reviewed the literature, designed the study, collected and analyzed data, organized the writing, and wrote the manuscript. A.R. collected and analyzed data. J.B.K. reviewed the literature

and designed the study. J.B.P. and V.Ø.T. collected data. H.T.S. conceived the study idea, reviewed the literature, designed the study, and collected data. C.R.H. conceived the study idea, reviewed the literature, and designed the study. R.W.T. conceived the study idea, reviewed the literature, designed the study, organized the writing, and is the guarantor. All authors interpreted the findings and edited and approved the final version of the manuscript.

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